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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,315	03/30/2004	Mechthild Rieping	7909/81000	1764

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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,315	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/15/2006 and 03/30/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQ Alignment*.

DETAILED ACTION

Application Status

1: In response to the previous Office action, a non-Final rejection (mailed on 05/16/2006), Applicants filed a response and amendment received on 09/15/2006. Said amendment cancelled Claims 1-12, added new Claims 13-22. Thus, Claims 13-22 are pending in the instant Office action.

Withdrawn-Objections to the Specification

2. Previous objection of the title is withdrawn by virtue of Applicant's amendment.

3. Previous objection of the Abstract is withdrawn by virtue of Applicant's amendment.

4. Previous objection of the Abstract, because it was not in one paragraph, is withdrawn by virtue of Applicant's amendment.

Withdrawn-Objections to the Drawing

5. Previous objection of the drawings for failing to comply with 37 CFR 1.84(p)(5) is withdrawn by virtue of Applicant's amendment.

New-Claim Objections

6. Claim 13 is objected to because of the following informalities: Claim 13 recites "starch cellulose" however, it should be ---starch, cellulose---, with addition of comma in

between as disclosed on page 7, lines 27-28. Also, Claim 13 needs conjunction "and" to connect method steps of a) and b).

New-Claim Rejections - 35 USC § 112

7. Claims 13-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 (claims 14-22 dependent therefrom) recites the limitation "overexpressed". However, the term "overexpressed" is a relative term, which renders the claim indefinite. The term "overexpressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

8. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 recites the limitation "overexpresses". However, the term "overexpresses" is a relative term, which renders the claim indefinite. The term "overexpresses" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

9. Claims 21 and 22 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Claim 4 recites the limitation "the thrABC operon" or "the tdh gene". There is insufficient antecedent basis for this limitation in the claim. It is unclear if the claims are limited to the one species disclosed in the specification (see pages 12-15) or to any gene from other organism. Clarification is required.

10. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitation "expression reduced". However, the term "expression reduced" is a relative term, which renders the claim indefinite. The term "expression reduced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

11. Claims 13-16 and 18-22 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a process for the production of an L-amino acid comprising fermenting a bacterium comprising an overexpressed endogenous DNA sequence encoding the galactose-proton symporter protein.

This rejection is a new rejection necessitated by the amendment.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification discloses only a single representative species of the recited genus of an bacteria, i.e., an E. coli transformed with an expression vector encoding SEQ ID NO: 4 optionally where the E. coli has been transformed with an expression vector comprising a thrABC operon and optionally wherein the E. coli has a deleted tdh gene. However, the breadth of claims 13-16 and 18-22 include using a genus of bacterial host cells having any modification to the bacteria that results in overexpressed DNA, optionally wherein the host cell has any modification to

overexpress a thrABC operon or reduce expression of a tdh gene. As such the claims encompass the use of widely variant species of bacteria modified to overexpress a DNA encoding SEQ ID NO: 4 and optionally overexpress a thrABC operon or reduces expression of a tdh gene. It is unpredictable as to those modifications that can make bacteria to achieve DNA overexpression or reduced expression. According to MPEP 2163, for inventions in an unpredictable art, adequate description of a genus encompassing widely variant species cannot be achieved by disclosing only a single species within the genus. Thus, one skilled in the art would recognize that applicant was not in possession of the invention.

The applicant argues that the amended claims are limited to exclude a "catalytic activity is altered are no longer part of the claims" (see Argument/Remark page 11 lines 1-3). However, this is not found persuasive because, for reasons noted above, the specification fails to adequately describe the genus of bacteria used in the claimed method.

12. Claims 13-16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a process using an *E. coli* transformed with an expression vector encoding SEQ ID NO: 4, does not reasonably provide enablement for a process for the production of L-amino acid using any bacterium having any modification to achieve overexpression of a nucleic acid encoding SEQ ID NO: 4. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the

invention commensurate in scope with these claims.

This rejection is a new rejection necessitated by the amendment.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a process for the production of an L-amino acid using a bacterium with overexpression of the galactose-proton symporter having SEQ ID NO: 4 (Claim 13), additionally overexpressing the disclosed genes in Claim 21, or additionally attenuating the disclosed genes in Claim 22. However, the

breadth of claims includes a method of using any bacterium having any modification that results in overexpression of a DNA encoding SEQ ID NO: 4 in Claim 13 (Claims 14-16 dependent therefrom), additionally overexpression of the thrABC gene (previously elected species) in Claim 21 or additionally decreased expression of the tdh gene (previously elected species) in Claim 22 according to a disclosure of the instant specification. However, other than the use of an expression vector to impart DNA overexpression or gene deletion to achieve reduced expression, the instant specification discloses no direction or guidance on how to make any bacterium having any modification that results in increased or decreased gene expression. The specification discloses only a single working example of the recited bacterium, i.e., an E. coli transformed with an expression vector encoding SEQ ID NO: 4 optionally where the E. coli has been transformed with an expression vector comprising a thrABC operon and optionally wherein the E. coli has a deleted a tdh gene. Additionally, the prior art does not remedy the deficiencies of the specification with respect to making all modified bacteria s encompassed by the claims. Because of the complex nature of modifying a living organism, the unpredictability of increasing or decreasing DNA expression is high. For all of the above reasons, it would require undue experimentation to practice the full scope of the claimed methods.

New-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 13-14 and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002, as cited in the previous Office Action) as evidenced by Blattner et al. (1997, Science 277:1453-1474, as cited in the IDS). The instant claims are drawn to a process for the production of an L-amino acid of L-Thr, L-Ile, L-Val, L-Met, L-homoserine or L-Lys comprising: fermenting an Enterobacteriaceae family with overexpressed endogenous DNA encoding the galactose-proton symporter protein of SEQ ID NO: 4 in the media having a disclosed carbon source with additional limitations disclosed in claims 14 and 17-20. This is a NEW claim rejection necessitated by the amendment.

Applicant argues that the "Valle reference, there was no way to predict that there would be a direct correlation between galP expression and amino acid production prior to the time that the present application was filed". However, Valle et al. teach that elimination of PTS enhances OAA production and that since OAA is the precursor of Asp, Lys, Met, Ile, and Thr, production of these amino acids could be enhanced in a PTS-/glucose+ strain (paragraph 5, bottom). See also Figure 1. Thus, Valle et al. disclose a direct relationship of amino acid production with overexpression of GalP protein. Even if this relationship was not disclosed, according to MPEP 2112, discovery

of a new property does not make an invention patentably distinct and further states that an inherent feature need not be known at the time of the invention.

Also, applicant argues the "improvements in amino acid production are attributed to the inactivation of the PTS pathway" (see Argument/Remark page 12 lines 10-11), and "the reference never suggests that increasing galP activity in normal, i.e., PTS positive, bacteria would have the same effect" (see Argument/Remark page 12 lines 19-20) of "increased amount of amino acids during fermentation" (see Argument/Remark page 12 line 15). The applicant also argues that "Valle expressly suggests that galP$^-$ based transport is of no physiological relevance unless the PTS pathway is blocked". However, the claims do not require bacteria with a PTS$^+$ phenotype and Valle et al. also disclose "the deletion of the ptsHIcrr operon creates **a new situation**" (emphasis added) which "turns on the galP gene" (see §0034, line 12) as shown in the examples of Valle et al. using E. coli **Pts**$^-$/glucose$^+$ strain NF9/pBE7 described in previous office action.

Valle et al. disclose teachings as described in the previous office action (pp. 11-12) and teach a method of using an endogenous galP gene from E. coli which is identical to instant SEQ ID NO: 4 as shown in a SEQ Alignment (See attachment) as evidenced by Blattner et al. Valle et al. also disclose "Since OAA is the precursor of aspartate, lysine, methionine, isoleucine and threonine (see Fig. 1), production of any of the latter compounds could be enhanced in Pts-/glucose+ strain". Valle et al. also teach the use of glucose for growing the cells (see Example 8, §0098, page 11). The method of Valle would have inherently resulted in enriching L-Thr and isolation of an L-amino

acid as encompass by the claims. Thus, Valle et al. teach all method steps required by the instant claims 13-14 and 17-20.

14. Claims 13-14 and 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Hernandez-Montalvo et al. (2003 Sep. 20, Biotechnol Bioeng, Vol. 83, page 687-694) as evidenced by Blattner et al. (1997, Science 277:1453-1474, as cited in the IDS) and Lee et al. (2003, September, Journal of Bacteriology, vol. 185, p. 5442-5451). The instant claims are drawn to a process for the production of an L-amino acid of L-Thr, L-Ile, L-Val, L-Met, L-homoserine or L-Lys comprising: fermenting an Enterobacteriaceae family with overexpressed endogenous DNA encoding the galactose-proton symporter protein of SEQ ID NO: 4 in the media having a disclosed carbon source with additional limitations disclosed in claims 13-14 and 18-20. This is a NEW claim rejection necessitated by the amendment.

Hernandez-Montalvo et al. teach a method of making a plasmid "containing E. coli galP" and used to transform E. coli (see left column middle, page 687). The transformed E. coli (see Table 1), which is a derivative of strain W3110 (p. 689, left column, bottom), "was used to evaluate the roles of GalP" (see right column, bottom, page 688. The "Cells were grown in Luria-Bertani (LB) broth or LB agar plates" which comprises glucose, "for all the recombinant DNA techniques" (see right column bottom on page 688 to left column top on page 689) or in M9 minimal media comprising 0.2 glucose (see middle of left column, p. 690). Hernandez-Montalvo et al. teach "the effect of increased GalP" "on growth capacity with glucose for a PTS- strain, the transformed

strains, with plasmids carrying the trc promoter set controlling galP and glk expression" wherein the galP gene is overexpressed (page 691, right column, top) (see right column bottom, page 690). Thus, Hernandez-Montalvo et al. teach a process of inherent production of L-Thr as evidenced by Lee et al. who disclose E. coli strain W3110 produces L-threonine as shown in Table 5, page 5450. That E. coli Galp is identical to SEQ ID NO: 4 is evidenced by Blattner et al. (see attached Sequence Alignment). Thus, a Hernandez-Montalvo et al. meets all limitations of Claims 13-14 and 17-20.

New-Claim Rejections - 35 USC § 103

15. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002, as cited in the previous Office Action) in view of Debabov et al. (USP 6,132,999 published on Oct. 17, 2000, as cited in the previous Office Action). This is a NEW claim rejection necessitated by the amendment.

Valle et al. disclose the teachings as described above. As noted above, Valle et al. particularly teach L-Thr production could be enhanced in a Pts^-/$glucose^+$.

Valle et al. does not teach overexpression of the thrABC operon in the Pts^- /$glucose^+$ strain for L-Thr production.

Debabov et al. (2000) teach a process of improved amino acid production by transforming an E. coli with an expression vector comprising a threonine operon (thrABC), which overexpresses the thrABC gene product. Debavov et al. (2000) teach a process of making L-threonine by using E. coli BKIIM B-5318 in Example 1. The E.

coli BKIIM B-5318 has "plasmid pPRT614, which has threonine biosynthesis genes (thrA, B, and C)" as disclosed in the Abstract.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to increase expression of galP encoding galactose permease of Valle et al. and additionally overexpress thrABC operon of Debabov et al. by transforming the PTS-/glucose$^+$ E. coli of Valle with the expression vector encoding thrABC of Debabov et al. The motivation to do so is provided by Valle et al. who teaches the usefulness of cost-effective and efficient biosynthetic production of compounds or derivative" (see column 0003, lines 1-2) using the Pts$^-$/glucose$^+$ GalP strain of Valle et al. for producing L-Thr (paragraph 5, bottom) and that overexpession of thrABC operon results in enhanced L-Thr production as taught by Debabov. One would have had a reasonable expectation of success for overexpressing thrABC operon in the Pts$^-$/glucose$^+$ strain of Valle et al. because of the teachings of Debabov et al. and Valle et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

16. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002) in view of Debavov et al. (USP 5,705371 published on Jan. 6, 1998). This is a NEW claim rejection necessitated by the amendment.

Valle et al. disclose teachings as described above. As noted above, Valle et al. particularly teach that L-thr production could be enhanced in a Pts$^-$/glucose$^+$ strain.

Valle et al. does not teach attenuation of the tdh gene.

Debavov et al. (1998) teach a process of making L-threonine by attenuation of the tdh gene encoding a threonine dehydrogenase "engaged in degradation of L-threonine" (see column 2, lines 58-59). Debavov et al. (1998) teach "E. coli strain VNIIgenetika 472T23" having "insertion of transposon Tn5 into gene tdh " is "devoid completely of activity" of a threonine dehydrogenase (see column 2, line 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to attenuate the tdh gene of Debavov et al. (1998) in the Pts^-/$glucose^+$ strain of Valle et al. The motivation to do so is provided by Valle et al. and Debabov et al. (1998) who teach the usefulness of "the cost-effective and efficient biosynthtic production of compounds or derivative" (see §0003 lines 1-2) by increasing the production of L-amino acid in E. coli, that L-Thr production could be enhanced in a Pts^-/$glucose^+$ strain, and that attenuation of tdh attenuates production of a polypeptide that degrades L-Thr. One would have had a reasonable expectation of success for attenuating a tdh gene in the Pts^-/$glucose^+$ strain of Valle et al. because of the teachings of Debabov et al. and Valle et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Summary of Pending Issues

17. The following is a summary of the issues pending in the instant application:

a) Claim 13 is objected because of recitation of "starch cellulose" and it needs conjunction "and" to connect method steps of a) and b).

b) Claim 13-22 is newly rejected under 35 U.S.C. 112, second paragraph, because of recitation of the limitation "overexpressed".

c) Claim 21 is newly rejected under 35 U.S.C. 112, second paragraph, because of recitation of the limitation "overexpresses".

d) Claims 21 and 22 are newly rejected under of 35 U.S.C. 112, second paragraph, because of recitation of the limitation "the thrABC operon" or "the tdh gene".

e) Claim 22 is newly rejected under 35 U.S.C. 112, second paragraph, because of the term "expression reduced".

f) Claims 13-16 and 18-22 are newly rejected under 35 U.S.C. § 112, first paragraph, written description.

g) Claims 13-16 and 18-22 are newly rejected under 35 U.S.C. 112, first paragraph, scope of enablement.

h) Claims 13-16 and 18-20 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Valle et al. as evidenced by Lee et al.

i) Claims 13-14 and 17-20 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Hernandez-Montalvo et al. as evidenced by Blattner et al. and Lee et al.

j) Claim 21 is newly rejected under 35 U.S.C. 103(a).

k) Claim 22 is rejected under 35 U.S.C. 103(a).

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
November 16, 2006

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER

Draft #4

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 05/16/2006), Applicants filed a response and amendment received on 09/15/2006. Said amendment cancelled Claims 1-12, added new Claims 13-22. Thus, Claims 13-22 are pending in the instant Office action.

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between as disclosed on page 7, lines 27-28. Also, Claim 13 needs conjunction "and" to connect method steps of a) and b).

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which applicant regards as the invention. Claim 4 recites the limitation "the thrABC operon" or "the tdh gene". There is insufficient antecedent basis for this limitation in the claim. It is unclear if the claims are limited to the one species disclosed in the specification (see pages 12-15) or to any gene from other organism. Clarification is required.

10. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitation "expression reduced". However, the term "expression reduced" is a relative term, which renders the claim indefinite. The term "expression reduced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

11. Claims 13-16 and 18-22 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a process for the production of an L-amino acid comprising fermenting a bacterium comprising an overexpressed endogenous DNA sequence encoding the galactose-proton symporter protein.

This rejection is a new rejection necessitated by the amendment.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification discloses only a single representative species of the recited genus of an bacteria, i.e., an E. coli transformed with an expression vector encoding SEQ ID NO: 4 optionally where the E. coli has been transformed with an expression vector comprising a thrABC operon and optionally wherein the E. coli has a deleted tdh gene. However, the breadth of claims 13-16 and 18-22 include using a genus of bacterial host cells having any modification to the bacteria that results in overexpressed DNA, optionally wherein the host cell has any modification to

overexpress a thrABC operon or reduce expression of a tdh gene. As such the claims encompass the use of widely variant species of bacteria modified to overexpress a DNA encoding SEQ ID NO: 4 and optionally overexpress a thrABC operon or reduces expression of a tdh gene. It is unpredictable as to those modifications that can make bacteria to achieve DNA overexpression or reduced expression. According to MPEP 2163, for inventions in an unpredictable art, adequate description of a genus encompassing widely variant species cannot be achieved by disclosing only a single species within the genus. Thus, one skilled in the art would recognize that applicant was not in possession of the invention.

The applicant argues that the amended claims are limited to exclude a "catalytic activity is altered are no longer part of the claims" (see Argument/Remark page 11 lines 1-3). However, this is not found persuasive because, for reasons noted above, the specification fails to adequately describe the genus of bacteria used in the claimed method.

12. Claims 13-16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a process using an *E. coli* transformed with an expression vector encoding SEQ ID NO: 4, does not reasonably provide enablement for a process for the production of L-amino acid using any bacterium having any modification to achieve overexpression of a nucleic acid encoding SEQ ID NO: 4. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the

invention commensurate in scope with these claims.

This rejection is a new rejection necessitated by the amendment.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a process for the production of an L-amino acid using a bacterium with overexpression of the galactose-proton symporter having SEQ ID NO: 4 (Claim 13), additionally overexpressing the disclosed genes in Claim 21, or additionally attenuating the disclosed genes in Claim 22. However, the

breadth of claims includes a method of using any bacterium having any modification that results in overexpression of a DNA encoding SEQ ID NO: 4 in Claim 13 (Claims 14-16 dependent therefrom), additionally overexpression of the thrABC gene (previously elected species) in Claim 21 or additionally decreased expression of the tdh gene (previously elected species) in Claim 22 according to a disclosure of the instant specification. However, other than the use of an expression vector to impart DNA overexpression or gene deletion to achieve reduced expression, the instant specification discloses no direction or guidance on how to make any bacterium having any modification that results in increased or decreased gene expression. The specification discloses only a single working example of the recited bacterium, i.e., an E. coli transformed with an expression vector encoding SEQ ID NO: 4 optionally where the E. coli has been transformed with an expression vector comprising a thrABC operon and optionally wherein the E. coli has a deleted a tdh gene. Additionally, the prior art does not remedy the deficiencies of the specification with respect to making all modified bacteria s encompassed by the claims. Because of the complex nature of modifying a living organism, the unpredictability of increasing or decreasing DNA expression is high. For all of the above reasons, it would require undue experimentation to practice the full scope of the claimed methods.

New-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

B/c rejection of Hernandez ref is 102(a), should the 102(a) statute here as well?

Yes.

13. Claims 13-14 and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002, as cited in the previous Office Action) as evidenced by Blattner et al. (1997, Science 277:1453-1474, as cited in the IDS). The instant claims are drawn to a process for the production of an L-amino acid of L-Thr, L-Ile, L-Val, L-Met, L-homoserine or L-Lys comprising: fermenting an Enterobacteriaceae family with overexpressed endogenous DNA encoding the galactose-proton symporter protein of SEQ ID NO: 4 in the media having a disclosed carbon source with additional limitations disclosed in claims 14 and 17-20. This is a NEW claim rejection necessitated by the amendment.

Applicant argues that the "Valle reference, there was no way to predict that there would be a direct correlation between galP expression and amino acid production prior to the time that the present application was filed". However, Valle et al. teach that elimination of PTS enhances OAA production and that since OAA is the precursor of Asp, Lys, Met, Ile, and Thr, production of these amino acids could be enhanced in a PTS-/glucose+ strain (paragraph 5, bottom). See also Figure 1. Thus, Valle et al. disclose a direct relationship of amino acid production with overexpression of GalP protein. Even if this relationship was not disclosed, according to MPEP 2112, discovery of a new property does not make an invention patentably distinct and further states that an inherent feature need not be known at the time of the invention.

Also, applicant argues the "improvements in amino acid production are attributed to the inactivation of the PTS pathway" (see Argument/Remark page 12 lines 10-11), and "the reference never suggests that increasing galP activity in normal, i.e., PTS positive, bacteria would have the same effect" (see Argument/Remark page 12 lines 19-20) of "increased amount of amino acids during fermentation" (see Argument/Remark page 12 line 15). The applicant also argues that "Valle expressly suggests that galP based transport is of no physiological relevance unless the PTS pathway is blocked". However, the claims do not require bacteria with a PTS^+ phenotype and Valle et al. also disclose "the deletion of the ptsHIcrr operon creates **a new situation**" (emphasis added) which "turns on the galP gene" (see §0034, line 12) as shown in the examples of Valle et al. using E. coli **Pts^-**/$glucose^+$ strain NF9/pBE7 described in previous office action.

Valle et al. disclose teachings as described in the previous office action (pp. 11-12) and teach a method of using an endogenous galP gene from E. coli which is identical to instant SEQ ID NO: 4 as shown in a SEQ Alignment (See attachment) as evidenced by Blattner et al. Valle et al. also disclose "Since OAA is the precursor of aspartate, lysine, methionine, isoleucine and threonine (see Fig. 1), production of any of the latter compounds could be enhanced in Pts-/glucose+ strain". Valle et al. also teach the use of glucose for growing the cells (see Example 8, §0098, page 11). The method of Valle would have inherently resulted in enriching L-Thr and isolation of an L-amino acid as encompass by the claims. Thus, Valle et al. teach all method steps required by the instant claims 13-14 and 17-20.

14. Claims 13-14 and 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Hernandez-Montalvo et al. (2003 Sep. 20, Biotechnol Bioeng, Vol. 83, page 687-694) as evidenced by Blattner et al. (1997, Science 277:1453-1474, as cited in the IDS) and Lee et al. (2003, September, Journal of Bacteriology, vol. 185, p. 5442-5451). The instant claims are drawn to a process for the production of an L-amino acid of L-Thr, L-Ile, L-Val, L-Met, L-homoserine or L-Lys comprising: fermenting an Enterobacteriaceae family with overexpressed endogenous DNA encoding the galactose-proton symporter protein of SEQ ID NO: 4 in the media having a disclosed carbon source with additional limitations disclosed in claims 13-14 and 18-20. This is a NEW claim rejection necessitated by the amendment.

Hernandez-Montalvo et al. teach a method of making a plasmid "containing E. coli galP" and used to transform E. coli (see left column middle, page 687). The transformed E. coli (see Table 1), which is a derivative of strain W3110 (p. 689, left column, bottom), "was used to evaluate the roles of GalP" (see right column, bottom, page 688. The "Cells were grown in Luria-Bertani (LB) broth or LB agar plates" which comprises glucose, "for all the recombinant DNA techniques" (see right column bottom on page 688 to left column top on page 689) or in M9 minimal media comprising 0.2 glucose (see middle of left column, p. 690). Hernandez-Montalvo et al. teach "the effect of increased GalP" "on growth capacity with glucose for a PTS- strain, the transformed strains, with plasmids carrying the trc promoter set controlling galP and glk expression" wherein the galP gene is overexpressed (page 691, right column, top) (see right column bottom, page 690). Thus, Hernandez-Montalvo et al. teach a process of inherent

production of L-Thr as evidenced by Lee et al. who disclose E. coli strain W3110 produces L-threonine as shown in Table 5, page 5450. That E. coli Galp is identical to SEQ ID NO: 4 is evidenced by Blattner et al. (see attached Sequence Alignment). Thus, a Hernandez-Montalvo et al. meets all limitations of Claims 13-14 and 17-20.

New-Claim Rejections - 35 USC § 103

15. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002, as cited in the previous Office Action) in view of Debabov et al. (USP 6,132,999 published on Oct. 17, 2000, as cited in the previous Office Action). This is a NEW claim rejection necessitated by the amendment.

Valle et al. disclose the teachings as described above. As noted above, Valle et al. particularly teach L-Thr production could be enhanced in a Pts^-/$glucose^+$.

Valle et al. does not teach overexpression of the thrABC operon in the Pts^- /$glucose^+$ strain for L-Thr production.

Debabov et al. (2000) teach a process of improved amino acid production by transforming an E. coli with an expression vector comprising a threonine operon (thrABC), which overexpresses the thrABC gene product. Debavov et al. (2000) teach a process of making L-threonine by using E. coli BKIIM B-5318 in Example 1. The E. coli BKIIM B-5318 has "plasmid pPRT614, which has threonine biosynthesis genes (thrA, B, and C)" as disclosed in the Abstract.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to increase expression of galP encoding galactose permease of Valle et al. and additionally overexpress thrABC operon of Debabov et al. by transforming the PTS-/glucose$^+$ E. coli of Valle with the expression vector encoding thrABC of Debabov et al. The motivation to do so is provided by Valle et al. who teaches the usefulness of cost-effective and efficient biosynthetic production of compounds or derivative" (see column 0003, lines 1-2) using the Pts$^-$/glucose$^+$ GalP strain of Valle et al. for producing L-Thr (paragraph 5, bottom) and that overexpession of thrABC operon results in enhanced L-Thr production as taught by Debabov. One would have had a reasonable expectation of success for overexpressing thrABC operon in the Pts$^-$/glucose$^+$ strain of Valle et al. because of the teachings of Debabov et al. and Valle et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

16. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Valle et al. (USPAP 2002/0155521 published on Oct. 24, 2002) in view of Debavov et al. (USP 5,705371 published on Jan. 6, 1998). This is a NEW claim rejection necessitated by the amendment.

Valle et al. disclose teachings as described above. As noted above, Valle et al. particularly teach that L-thr production could be enhanced in a Pts$^-$/glucose$^+$ strain.

Valle et al. does not teach attenuation of the tdh gene.

Debavov et al. (1998) teach a process of making L-threonine by attenuation of the tdh gene encoding a threonine dehydrogenase "engaged in degradation of L-threonine" (see column 2, lines 58-59). Debavov et al. (1998) teach "E. coli strain VNIIgenetika 472T23" having "insertion of transposon Tn5 into gene tdh " is "devoid completely of activity" of a threonine dehydrogenase (see column 2, line 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to attenuate the tdh gene of Debavov et al. (1998) in the Pts^-/$glucose^+$ strain of Valle et al. The motivation to do so is provided by Valle et al. and Debabov et al. (1998) who teach the usefulness of "the cost-effective and efficient biosynthtic production of compounds or derivative" (see §0003 lines 1-2) by increasing the production of L-amino acid in E. coli, that L-Thr production could be enhanced in a Pts^-/$glucose^+$ strain, and that attenuation of tdh attenuates production of a polypeptide that degrades L-Thr. One would have had a reasonable expectation of success for attenuating a tdh gene in the Pts^-/$glucose^+$ strain of Valle et al. because of the teachings of Debabov et al. and Valle et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Summary of Pending Issues

17. The following is a summary of the issues pending in the instant application:

a) Claim 13 is objected because of recitation of "starch cellulose" and it needs conjunction "and" to connect method steps of a) and b).

b) Claim 13-22 is newly rejected under 35 U.S.C. 112, second paragraph, because of recitation of the limitation "overexpressed".

c) Claim 21 is newly rejected under 35 U.S.C. 112, second paragraph, because of recitation of the limitation "overexpresses".

d) Claims 21 and 22 are newly rejected under of 35 U.S.C. 112, second paragraph, because of recitation of the limitation "the thrABC operon" or "the tdh gene".

e) Claim 22 is newly rejected under 35 U.S.C. 112, second paragraph, because of the term "expression reduced".

f) Claims 13-16 and 18-22 are newly rejected under 35 U.S.C. § 112, first paragraph, written description.

g) Claims 13-16 and 18-22 are newly rejected under 35 U.S.C. 112, first paragraph, scope of enablement.

h) Claims 13-16 and 18-20 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Valle et al. as evidenced by Lee et al.

i) Claims 13-14 and 17-20 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Hernandez-Montalvo et al. as evidenced by Blattner et al. and Lee et al.

j) Claim 21 is newly rejected under 35 U.S.C. 103(a).

k) Claim 22 is rejected under 35 U.S.C. 103(a).

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
November 16, 2006

SEQ Alignment
10/812315

RESULT 2
GALP_ECOLI
ID   GALP_ECOLI   STANDARD;   PRT;   464 AA.
AC   P0AEP1; P37021;
DT   20-DEC-2005, integrated into UniProtKB/Swiss-Prot.
DT   20-DEC-2005, sequence version 1.
DT   07-MAR-2006, entry version 5.
DE   Galactose-proton symporter (Galactose transporter).
GN   Name=galP; OrderedLocusNames=b2943;
OS   Escherichia coli.
OC   Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
OC   Enterobacteriaceae; Escherichia.
OX   NCBI_TaxID=562;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [GENOMIC DNA], AND CHARACTERIZATION.
RA   Roberts P.E.;
RL   Thesis (1992), University of Cambridge, United Kingdom.
RN   [2]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RC   STRAIN=K12 / MG1655;
RX   MEDLINE=97426617; PubMed=9278503; DOI=10.1126/science.277.5331.1453;
RA   Blattner F.R., Plunkett G. III, Bloch C.A., Perna N.T., Burland V.,
RA   Riley M., Collado-Vides J., Glasner J.D., Rode C.K., Mayhew G.F.,
RA   Gregor J., Davis N.W., Kirkpatrick H.A., Goeden M.A., Rose D.J.,
RA   Mau B., Shao Y.;
RT   "The complete genome sequence of Escherichia coli K-12.";
RL   Science 277:1453-1474(1997).
RN   [3]
RP   SUBCELLULAR LOCATION.
RC   STRAIN=K12 / MG1655;
RX   PubMed=15919996; DOI=10.1126/science.1109730;
RA   Daley D.O., Rapp M., Granseth E., Melen K., Drew D., von Heijne G.;
RT   "Global topology analysis of the Escherichia coli inner membrane
RT   proteome.";
RL   Science 308:1321-1323(2005).
CC   -!- FUNCTION: Uptake of galactose across the boundary membrane with
CC   the concomitant transport of protons into the cell (symport
CC   system).
CC   -!- SUBCELLULAR LOCATION: Bacterial cell inner membrane; multi-pass
CC   membrane protein.
CC   -!- SIMILARITY: Belongs to the major facilitator superfamily. Sugar
CC   transporter family.
CC   --
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   --
DR   EMBL; U28377; AAA69110.1; -; Genomic_DNA.
DR   EMBL; U00096; AAC75980.1; -; Genomic_DNA.
DR   PIR; F65079; F65079.
DR   GenomeReviews; U00096_GR; b2943.
DR   EchoBASE; EB2068; -.
DR   EcoGene; EG12148; galP.
DR   BioCyc; EcoCyc:GALP-MONOMER; -.
DR   LinkHub; P37021; -.
DR   PROSITE; PS50850; MFS; 1.
DR   PROSITE; PS00216; SUGAR_TRANSPORT_1; 1.
DR   PROSITE; PS00217; SUGAR_TRANSPORT_2; 1.
KW   Complete proteome; Inner membrane; Membrane; Sugar transport; Symport;
KW   Transmembrane; Transport.

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FT   TRANSMEM     57     77       2 (Potential).
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FT   TRANSMEM    113    133       4 (Potential).
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Qy        121 VASYTAPLYLSEIAPEKIRGSMISMYQLMITIGILGAYLSDTAFSYTGAWRWMLGVIIIP 180
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Qy        181 AILLLIGVFFLPDSPRWFAAKRRFVDAERVLLRLRDTSAEAKRELDEIRESLQVKQSGWA 240
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Qy        241 LFKENSNFRRAVFLGVLLQVMQQFTGMNVIMYYAPKIFELAGYTNTTEQMWGTVIVGLTN 300
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Qy        361 GFAMSAGPLIWVLCSEIQPLKGRDFGITCSTATNWIANMIVGATFLTMLNTLGNANTFWV 420
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RESULT 1
AAS46267
ID   AAS46267 standard; DNA; 12354 BP.
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AC   AAS46267;
XX
DT   18-DEC-2001  (first entry)
XX
DE   DNA encoding novel mar regulated protein (NIMR) #36.
XX
KW   mar regulated polypeptide; NIMR; microbial infection; antibacterial; ds.
XX
OS   Escherichia coli.
XX
PN   WO200170776-A2.
XX
PD   27-SEP-2001.
XX
PF   08-MAR-2001; 2001WO-US007478.
XX
PR   10-MAR-2000; 2000US-0188362P.
XX
PA   (TUFT ) TUFTS COLLEGE.
XX
PI   Levy SB,  Barbosa TM,  Alekshun MN;
XX
DR   WPI; 2001-602769/68.
DR   P-PSDB; AAU29368.
XX
PT   Identifying compounds that modulate a newly identified mar regulated
PT   polypeptide activity, useful as antimicrobial compounds, involves
PT   contacting the polypeptide with a test compound.
XX
PS   Disclosure; Page 424-432; 526pp; English.
XX
CC   The invention relates to a method of identifying compounds that modulate
CC   a newly identified mar regulated (NIMR) polypeptide activity. The method
CC   comprises contacting an NIMR polypeptide with a test compound under
CC   interaction conditions, determining the ability of the compound to
CC   modulate the activity or expression of the polypeptide, and selecting the
CC   modulators. NIMR nucleic acids and polypeptides are used in the treatment
CC   of microbial infections, and in screening for modulators of NIMR
CC   expression and activity. These modulators can be used to reduce the
CC   infectivity of a microbe on a surface, and the virulence of a microbe in
CC   a subject suffering from an infection. AAS46232-AAS46278 represent
CC   Escherichia coli NIMR coding sequences of the invention
XX
SQ   Sequence 12354 BP; 3031 A; 3249 C; 3190 G; 2884 T; 0 U; 0 Other;

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  Best Local Similarity   99.7%;  Pred. No. 0;
  Matches 1441;  Conservative    0;  Mismatches    5;  Indels    0;  Gaps    0;

Qy          1 CACAATCTAGATAAACCATATTGGAGGGCATCATGCCTGACGCTAAAAAACAGGGGCGGT 60
              ||||||  | ||  ||||||||||||||||||||||||||||||||||||||||||||
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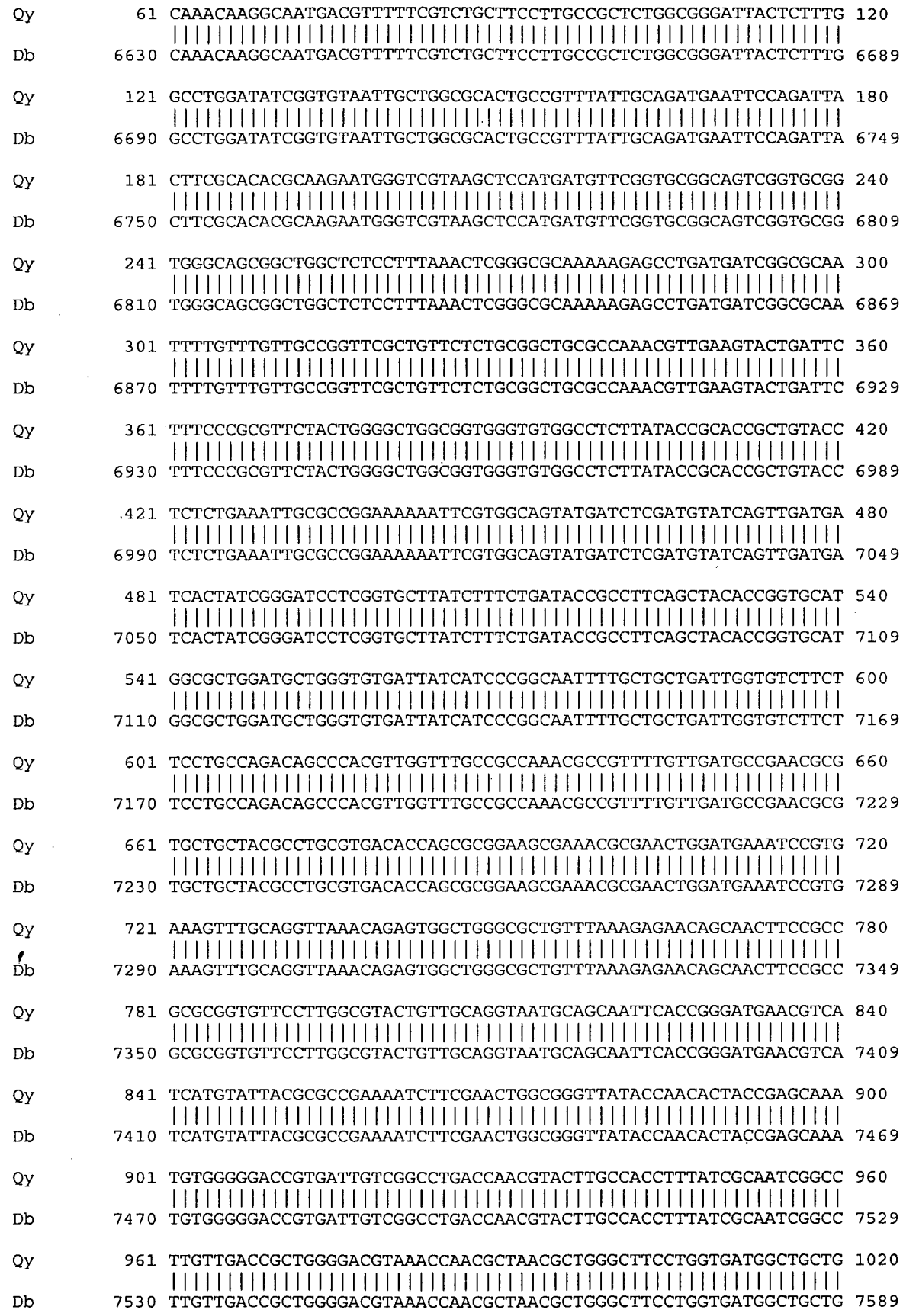

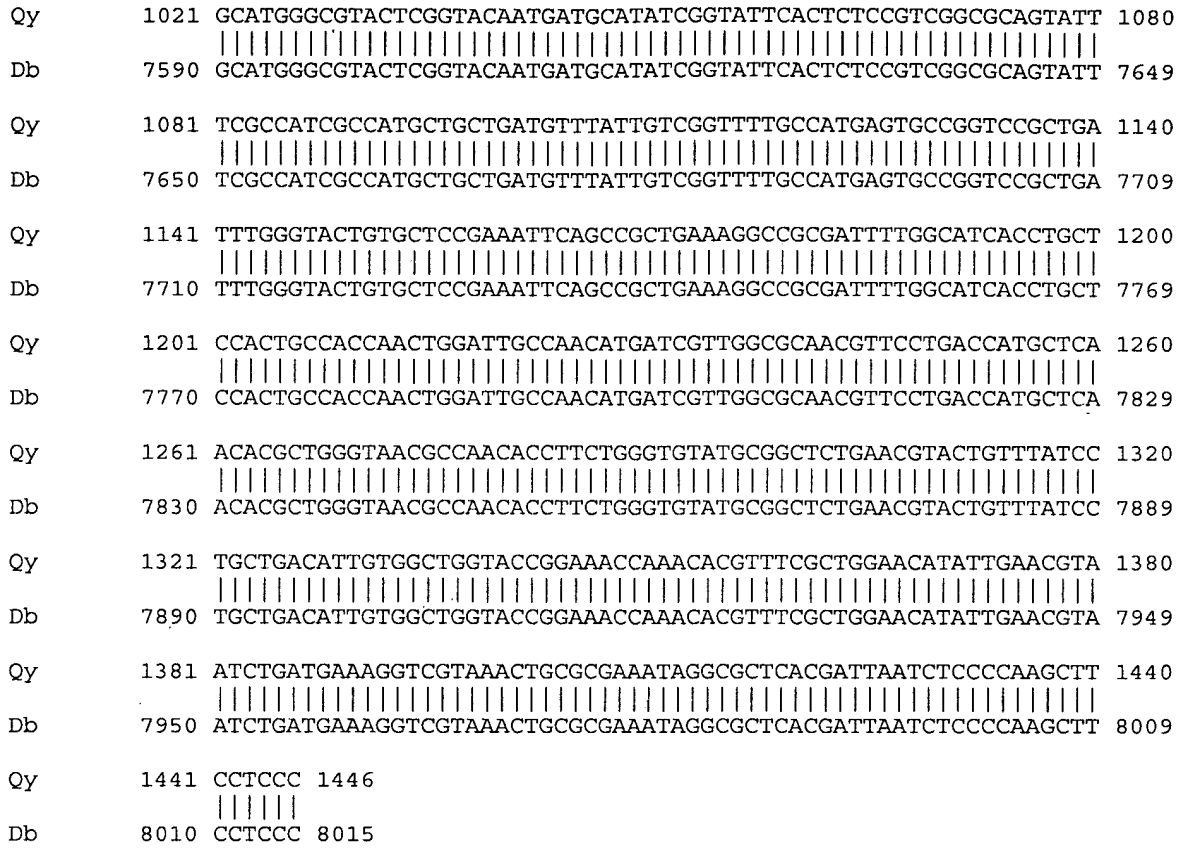
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SOURCE Escherichia coli K12
ORGANISM Escherichia coli K12
Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
Enterobacteriaceae; Escherichia.
REFERENCE 1 (bases 1 to 4639675)
AUTHORS Blattner,F.R., Plunkett,G., Bloch,C.A., Perna,N.T., Burland,V.,
Riley,M., Collado-Vides,J., Glasner,J.D., Rode,C.K., Mayhew,G.F.,
Gregor,J., Davis,N.W., Kirkpatrick,H.A., Goeden,M.A., Rose,D.J.,
Mau,B. and Shao,Y.
TITLE The complete genome sequence of Escherichia coli K-12
JOURNAL Science 277 (5331), 1453-1474 (1997)
PUBMED 9278503
REFERENCE 2 (bases 1 to 4639675)
AUTHORS Riley,M., Abe,T., Arnaud,M.B., Berlyn,M.K., Blattner,F.R.,
Chaudhuri,R.R., Glasner,J.D., Horiuchi,T., Keseler,I.M., Kosuge,T.,
Mori,H., Perna,N.T., Plunkett,G. III, Rudd,K.E., Serres,M.H.,
Thomas,G.H., Thomson,N.R., Wishart,D. and Wanner,B.L.
TITLE Escherichia coli K-12: a cooperatively developed annotation
snapshot--2005
JOURNAL (er) Nucleic Acids Res. 34 (1), 1-9 (2006)
PUBMED 16397293
REFERENCE 3 (bases 1 to 4639675)
AUTHORS Arnaud,M., Berlyn,M.K.B., Blattner,F.R., Galperin,M.Y.,
Glasner,J.D., Horiuchi,T., Kosuge,T., Mori,H., Perna,N.T.,
Plunkett,G. III, Riley,M., Rudd,K.E., Serres,M.H., Thomas,G.H. and
Wanner,B.L.
TITLE Workshop on Annotation of Escherichia coli K-12
JOURNAL Unpublished
REMARK Woods Hole, Mass., on 14-18 November 2003 (sequence corrections)
REFERENCE 4 (bases 1 to 4639675)
AUTHORS Glasner,J.D., Perna,N.T., Plunkett,G. III, Anderson,B.D.,
Bockhorst,J., Hu,J.C., Riley,M., Rudd,K.E. and Serres,M.H.
TITLE ASAP: Escherichia coli K-12 strain MG1655 version m56
JOURNAL Unpublished
REMARK ASAP download 10 June 2004 (annotation updates)
REFERENCE 5 (bases 1 to 4639675)
AUTHORS Hayashi,K., Morooka,N., Mori,H. and Horiuchi,T.
TITLE A more accurate sequence comparison between genomes of Escherichia
coli K12 W3110 and MG1655 strains
JOURNAL Unpublished
REMARK GenBank accessions AG613214 to AG613378 (sequence corrections)
REFERENCE 6 (bases 1 to 4639675)
AUTHORS Perna,N.T.
TITLE Escherichia coli K-12 MG1655 yqiK-rfaE intergenic region, genomic
sequence correction
JOURNAL Unpublished
REMARK GenBank accession AY605712 (sequence corrections)
REFERENCE 7 (bases 1 to 4639675)
AUTHORS Rudd,K.E.
TITLE A manual approach to accurate translation start site annotation: an
E. coli K-12 case study
JOURNAL Unpublished
REFERENCE 8 (bases 1 to 4639675)
AUTHORS Blattner,F.R. and Plunkett,G. III.
TITLE Direct Submission

JOURNAL Submitted (16-JAN-1997) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
REFERENCE 9 (bases 1 to 4639675)
AUTHORS Blattner,F.R. and Plunkett,G. III.
TITLE Direct Submission
JOURNAL Submitted (02-SEP-1997) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
REFERENCE 10 (bases 1 to 4639675)
AUTHORS Plunkett,G. III.
TITLE Direct Submission
JOURNAL Submitted (13-OCT-1998) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
REFERENCE 11 (bases 1 to 4639675)
AUTHORS Plunkett,G. III.
TITLE Direct Submission
JOURNAL Submitted (10-JUN-2004) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
REMARK Sequence update by submitter
REFERENCE 12 (bases 1 to 4639675)
AUTHORS Plunkett,G. III.
TITLE Direct Submission
JOURNAL Submitted (07-FEB-2006) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
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ORIGIN
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NCBI | NLM | NIH

Sequences producing significant alignments:	Score (Bits)	E Value
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gi|48994873|gb|U00096.2| Escherichia coli K12 MG1655, complete g	2841	0.0
gi|882431|gb|U28377.1|ECU28377 Escherichia coli K-12 genome; app	2841	0.0
gi|81244029|gb|CP000036.1| Shigella boydii Sb227, complete genom	2785	0.0

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gi|81239530|gb|CP000034.1|  Shigella dysenteriae Sd197, complete   2714    0.0
gi|110341805|gb|CP000247.1|  Escherichia coli 536, complete genom  2698    0.0
gi|26111730|gb|AE014075.1|  Escherichia coli CFT073, complete gen  2690    0.0
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 Features in this part of subject sequence:
   D-galactose transporter

 Score = 2841 bits (1433),  Expect = 0.0
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Sbjct  3088181  CGCCAACACCTTCTGGGTGTATGCGGCTCTGAACGTACTGTTTATCCTGCTGACATTGTG  3088240

Query  1334     GCTGGTACCGGAAACCAAACACGTTTCGCTGGAACATATTGAACGTAATCTGATGAAAGG  1393
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  3088241  GCTGGTACCGGAAACCAAACACGTTTCGCTGGAACATATTGAACGTAATCTGATGAAAGG  3088300

Query  1394     TCGTAAACTGCGCGAAATAGGCGCTCACGATTAATCTCCCCAAGCTTCCTCCC  1446
                ||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  3088301  TCGTAAACTGCGCGAAATAGGCGCTCACGATTAATCTCCCCAAGCTTCCTCCC  3088353
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